

In the Specification:

Please amend the specification as shown:

Insert the Sequence Listing submitted herewith.

Please delete paragraph [0068] and replace it with the following paragraph:

[0068] In particular embodiments, the oligonucleotide binds to one or more viral proteins; the sequence of the oligonucleotide (or a portion thereof, e.g., at least ½) is derived from a viral genome; the activity of an oligonucleotide with a sequence derived from a viral genome is not superior to a random oligonucleotide or a random oligonucleotide of the same length; the oligonucleotide includes a portion complementary to a viral sequence and a portion not complementary to a viral sequence; the sequence of the oligonucleotide is derived from a viral packaging sequence or other viral sequence involved in an aptameric interaction; unless otherwise indicated, the sequence of the oligonucleotide includes A(x), C(x), G(x), T(x), AC(x), AG(x), AT(x), CG(x), CT(x), or GT(x), where x is 2, 3, 4, 5, 6, ... 60 ... 120 **(SEQ ID NOS 27-36, respectively)** (in particular embodiments the oligonucleotide is at least 29, 30, 32, 34, 36, 38, 40, 46, 50, 60, 70, 80, 90, 100, 110, or 120 nucleotides in length or the length of the specified repeat sequence is at least a length just specified); the oligonucleotide is single stranded (RNA or DNA); the oligonucleotide is double stranded (RNA or DNA); the oligonucleotide includes at least one Gquartet or CpG portion; the oligonucleotide includes a portion complementary to a viral mRNA and is at least 29, 37, or 38 nucleotides in length (or other length as specified above); the oligonucleotide includes at least one non-Watson-Crick oligonucleotide and/or at least one nucleotide that participates in non-Watson-Crick binding with another nucleotide; the oligonucleotide is a random oligonucleotide, the oligonucleotide is a randomer or includes a randomer portion, e.g., a randomer portion that has a length as specified above for oligonucleotide length; the oligonucleotide is linked or conjugated at one or more nucleotide residues to a molecule that modifies the characteristics of the oligonucleotide, e.g. to provide higher stability (such as stability in serum or stability in a particular solution), lower serum interaction, higher cellular uptake, higher viral protein interaction, improved ability to be formulated for delivery, a detectable signal, improved pharmacokinetic properties, specific tissue distribution, and/or lower toxicity.

Please delete paragraph [000143] and replace it with the following paragraph:

[00143] Figure 37. (A) IC50 values generated from a plaque reduction assay conducted in VERO cells using HSV-1 (strain KOS). Infected cells are treated with increasing concentrations of REP 2006 (N40), REP 2028 (G40) (SEQ ID NO: 21), REP 2029 (A40) (SEQ ID NO: 20), REP 2030 (T40) (SEQ ID NO: 23), and REP 2031 (C40) (SEQ ID NO: 22) to generate IC50 values. (B) HSV-1 PRA generated IC50 values of the following: N40 (REP 2006), AC20 (SEQ ID NO: 24) (REP 2055, TC20 (SEQ ID NO: 25) (REP 2056), or AG20 (SEQ ID NO: 26) (REP 2057).

Please delete paragraph [000199] and replace it with the following paragraph:

[00199] We monitored the ability of PS-ODNs of different sequences to interact with several viral lysates. In each case, a 20-mer PS-ODN is labeled at the 3' end with FITC as previously described herein. The PS-ODNs tested consisted of A20 (SEQ ID NO: 12), T20 (SEQ ID NO: 15), G20 (SEQ ID NO: 13), C20 (SEQ ID NO: 14), AC10 (SEQ ID NO: 16), AG10 (SEQ ID NO: 17), TC10 (SEQ ID NO: 18), TG10 (SEQ ID NO: 19), REP 2004 and REP 2017. Each of these sequences is diluted to 4nM in assay buffer and incubated in the presence of 1ug of HSV-1, HIV-1 or RSV lysate. Interaction is measured by fluorescence polarization.

Please delete paragraph [000200] and replace it with the following paragraph:

[00200] The profile of interaction with all sequences tested is similar in all viral lysates, indicating that the nature of the binding interaction is very similar. Within each lysate, the PS-ODNs of uniform composition (A20 (SEQ ID NO:12), G20 (SEQ ID NO:13), T20 (SEQ ID NO:15), C20 (SEQ ID NO:14)) were the weakest interactors with A20 (SEQ ID NO:12) being the weakest interactor of these by a significant margin. For the rest of the PS-ODNs tested, all of them displayed a similar, strong interaction with the exception of TG10 (SEQ ID NO:19), which consistently displayed the strongest interaction in each lysate (see figure 35).

Please delete paragraph [00302] and replace it with the following paragraph:

[00302] To determine if non-specific sequence composition has an effect on ON antiviral activity, several PS-ODNs of equivalent size but differing in their sequence composition were tested for anti-HSV1 activity in the HSV-1 PRA. The PS-ODNs tested were REP 2006 (N20), REP 2028 (G40)(SEQ ID NO: 21), REP 2029 (A40) (SEQ ID NO: 20), REP 2030 (T40) (SEQ ID NO: 23) and REP 2031 (C40) (SEQ ID NO: 22).. The IC50 values generated from the HSV-1 PRA (see figure 37) show that REP 2006 (N40) was clearly the most active of all sequences tested while REP 2029 (A40) (SEQ ID NO: 20) was the least active. We also note that, all the other PS-ODNs were significantly less active than N40 with their rank in terms of efficacy being N40>C40 (SEQ ID NO: 22)>T40> (SEQ ID NO: 23) A40 (SEQ ID NO: 20)>>G40 (SEQ ID NO: 21).

Please delete paragraph [00303] and replace it with the following paragraph:

[00303] We also tested the efficacy of different PS ODNs having varying sequence composition with two different nucleotides (see figure 37b). The PS-ODN randomer (REP 2006) was significantly more efficacious against HSV-1 than AC20 (SEQ ID NO: 24)(REP 2055), TC20 (SEQ ID NO: 25) (REP 2056) or AG20 (SEQ ID NO: 26) (REP 2057) with their efficacies ranked as follows: N40>AG(20)(SEQ ID NO: 26)>AC(20)(SEQ ID NO: 24)>TC(20)(SEQ ID NO: 25). This data suggests that although the anti-viral effect is non-sequence complementary, certain non-specific sequence compositions (ie C40 (SEQ ID NO: 22) and N40) have the most potent anti-viral activity. We suggest that this phenomenon can be explained by the fact that, while retaining intrinsic protein binding ability, sequences like C40 (SEQ ID NO: 22), A40 (SEQ ID NO: 20), T40 (SEQ ID NO: 23) and G40 (SEQ ID NO: 21) bind fewer viral proteins with high affinity, probably due to some restrictive tertiary structure formed in these sequences. On the other hand, due to the random nature of N40, it retains its ability to bind with high affinity to a broad range of anti-viral proteins which contributes to its robust anti-viral activity.

TABLE 1 – DESCRIPTION OF OLIGONUCLEOTIDES

DLMR251851.1

REP 2013 10mer randomer
SEQUENCE N N N N N N N N N N
no modification

REP 2014 20mer randomer
SEQUENCE N N N N N N N N N N N N N N N N N N
no modification

REP 2015 40mer randomer
SEQUENCE N
no modification

REP 2016 10mer random sequence
SEQUENCE T C C G A A G A C G (SEQ ID NO: 4)
PS ? ? ? ? ? ? ? ? ?

REP 2017 20mer random sequence
SEQUENCE A C A C C T C C G A A G A C G A T A A C (SEQ ID NO: 5)
PS ? ? ? ? ? ? ? ? ? ? ? ? ? ? ? ? ? ?

REP 2018 40mer random sequence
SEQUENCE C T A C A G A C A T A C A C C T C C G A A G A C G A T A A C A C T A G A C A T A (SEQ ID NO: 6)
PS ?

REP 2019 10mer sequence centered around start codon of HSV-1 IE110 protein (NCBI accession # X04614)
SEQUENCE C C C C C A T G G A (SEQ ID NO: 7)
PS ? ? ? ? ? ? ? ? ?

REP 2020 20mer sequence centered around start codon of HSV-1 IE110 protein (NCBI accession # X04614)
SEQUENCE T A C G A C C C C A T G G A G C C C C (SEQ ID NO: 8)
PS ? ? ? ? ? ? ? ? ? ? ? ? ? ? ? ? ? ?

REP 2021 40mer sequence centered around start codon of HSV-1 IE110 protein (NCBI accession # X04614)
SEQUENCE T C C A G C C G C A T A C G A C C C C A T G G A G C C C C C G C C C G G A G C (SEQ ID NO: 9)
PS ?

REP 2024 40mer randomer
SEQUENCE N
PS ?
2-O Me ? ? ? ? ? ? ? ?

REP 2026 40mer randomer
SEQUENCE N
PCH3 ? ? ? ? ? ? ? ?

REP 2036 21mer commercially marketed antisense against CMV (vitravine/fomvirisen) SYNTHESIZED INTERNALLY
SEQUENCE G C G T T T G C T C T T C T T C T T G C G (SEQ ID NO: 10)
PS ? ? ? ? ? ? ? ? ? ? ? ? ? ? ? ? ? ? ?

REP 2036 © 21mer commercially marketed antisense against CMV (vitravine/fomvirisen) COMMERCIAL PRODUCT (cGMP)
SEQUENCE G C G T T T G C T C T T C T T C T T G C G (SEQ ID NO: 11)
PS ? ? ? ? ? ? ? ? ? ? ? ? ? ? ? ? ? ? ?

A20 20 mer
SEQUENCE A A A A A A A A A A A A A A A A A A -FITC (SEQ ID NO: 12)
PS ? ? ? ? ? ? ? ? ? ? ? ? ? ? ? ? ? ?

G20 20 mer
SEQUENCE G G G G G G G G G G G G G G G G G G -FITC (SEQ ID NO: 13)
PS ? ? ? ? ? ? ? ? ? ? ? ? ? ? ? ? ? ?

C20 20 mer
SEQUENCE C C C C C C C C C C C C C C C C C C -FITC (SEQ ID NO: 14)
PS ? ? ? ? ? ? ? ? ? ? ? ? ? ? ? ? ? ?

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